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Stüve-Wiedemann Syndrome: Update and Historical Footnote

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Stüve-Wiedemann syndrome (SWS) is, at last, beginning to emerge from the shadows of campomelic syndrome as a nosologically and, presumably, causally-distinct entity, first delineated in 1971 on the basis of 2 affected sisters. The fact that these sisters had an affected double first cousin supports autosomal-recessive inheritance of SWS.

KEY WORDS: multiple congenital anomalies syndrome, skeletal dysplasia, congenital bowing of long bones, respiratory insufficiency, malignant hyperthermia, autosomal-recessive inheritance

INTRODUCTION

In 1971 we described 2 sisters with congenital bowing of the long bones and other abnormalities [Stüve and Wiedemann, 1971a,b]. We interpreted the bowing as a nonspecific phenomenon, but postulated that our cases may represent a specific condition within the heterogeneous group of congenital bowing disorders.

Spranger et al. [1970] called attention to another specific bowing syndrome, and in the following year Maroteaux et al. [1971] delineated this condition as campomelic syndrome. Subsequently, these authors published further studies on the campomelic syndrome as a distinct entity [Maroteaux, 1973; Hall and Spranger, 1980b; Houston et al., 1983; Spranger and Maroteaux, 1990a]. Hall and Spranger [1980a] discussed the nosology of congenital bowing of the long bones with phenotype analysis of 13 undiagnosed cases. Subsequently, this condition was found to be due to a SOX9 mutation [Foster et al., 1994; Wagner et al., 1994; Kwok et al., 1995].

Our own cases were soon accepted as examples of a separate entity and called Stüve-Wiedemann dysplasia or syndrome (SWS) [Maroteaux, personal communication; Hall and Spranger, 1980a; Gorlin et al., 1990; Spranger and Maroteaux, 1990b]; this syndrome is registered in the International Classification of Osteochondrodysplasias [Spranger, 1992]. However, to date, many workers in the field do not make a distinction between this and campomelic syndrome.

Our initial publication [Stüve and Wiedemann, 1971a] was complicated by the political realities of pediatrics in a divided Germany. Dr. Annemarie Stüve was a student and scientific coworker of the esteemed Professor Albrecht Peiper at the University Department of Pediatrics in Leipzig; subsequently she became the pediatrician-in-chief of an independent children's unit in Saxonia. It was there that she observed "our" cases and referred them to me for consultation. After this collaboration we planned to publish these observations together. However, at the beginning of 1970 I received an anonymous message apologizing for having to decline collaboration and stating that it was not permitted to mention her (Dr. Stüve's) name. A strict prohibition was being enforced against all noncontrolled scientific collaboration with persons in the Federal Republic of Germany. This policy apparently remained in effect in the former "German Democratic Republic" until its demise in 1989. I proceeded with publication alone, but placed the name of Dr. Annemarie Stüve first on the final paper.

CLINICAL REPORT

At this time we give fuller documentation of these patients. The pedigree is in Figure 1. Clinical aspects are illustrated in Figures 2 and 3 (patient 2), and radiological aspects of patients 1 and 2 are shown in Figures 4–7.

The girls had limited mobility of the elbows and long fingers. Several fingers in both cases were congenitally flexed (camptodactyly) with ulnar deviation. Radiologically there were normal clavicles, a broad coracoid

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Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

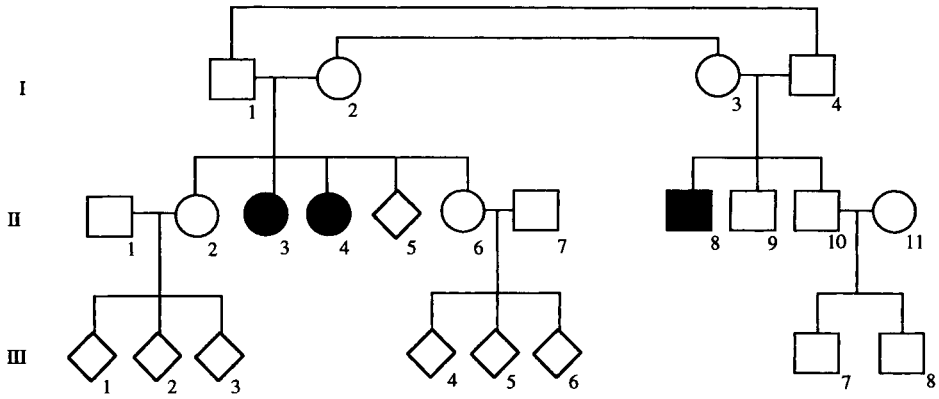

Fig. 1. Pedigree of our patients. Note involvement of double first cousins.

process bilaterally, relatively long scapulae, and relatively thin ribs (12 pairs) in both cases. As far as visible, the cervical spine of patient 1 was normal. The lumbar spine of patient 2 was normal. The ilia were relatively small, and the pubic and ischial bones were relatively broad. Autopsy in both children showed pneumonia; a further finding in both cases was a lacunar skull.

Patient 1 died on the tenth day of life of respiratory insufficiency with multiple apneic spells; patient 2 manifested deglutition difficulties, and during her last 2 days hyperthermia as high as 41°C; she died on the fifth day of life.

The young, healthy, nonconsanguineous parents of these babies and their first-born daughter were clinically and radiologically normal. The baby boy of the mother's sister had identical congenital flexion contractures of fingers and toes and also died of neonatal respiratory insufficiency. It seems very probably that this infant also had Stüve-Wiedemann syndrome.

DISCUSSION

After a quarter century of experience, it is possible to assert that Stüve-Wiedemann syndrome (SWS) is sufficiently unique to constitute an entity different from campomelic syndrome. However, to this day some data bases (e.g., OMIM [McKusick, 1994]) cite the two initial publications on SWS either under Weismann-Netter (112350) or camptomelic (sic) (211970) syndrome. In the nosology of campomelic syndrome, Gorlin et al. [1990] state, "Still a different, probably autosomal recessively inherited disorder was described by Stüve and Wiedemann . . . the feet were abnormally positioned. There was fatal respiratory distress." Except for OSSUM, SWS is not found in the other data bases, or else appears nonspecifically in lengthy lists of disorders associated with congenital bowing of the limbs (long bones). In OSSUM, SWS is syndrome 1860 with two references [Stüve et al. (sic), 1971; Spranger et al., 1990 (sic)], and a list of 29 traits useful for matching (making) this diagnosis. The most

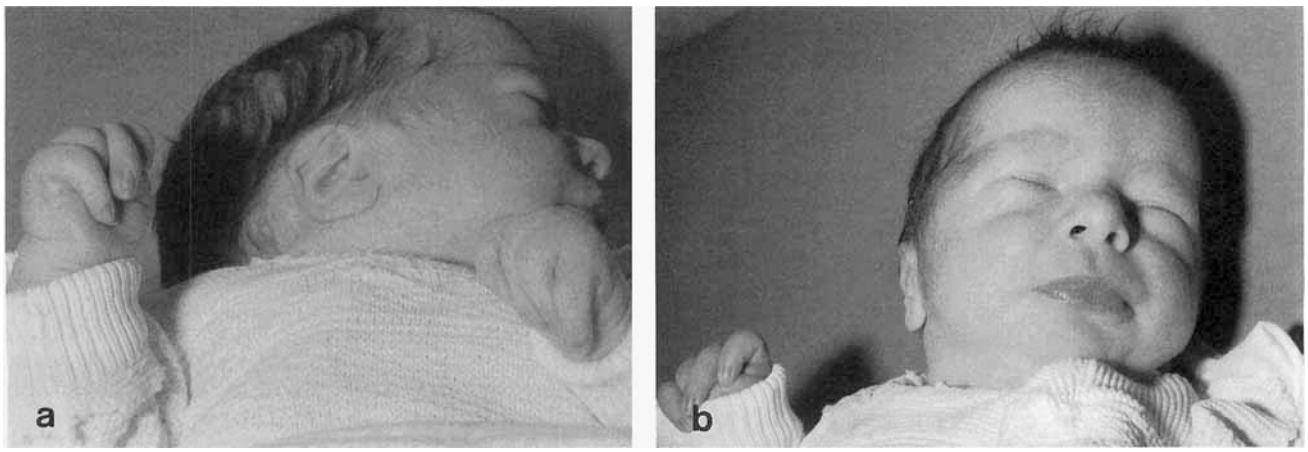

Fig. 2. **a,b:** Patient 2. Face, head, and hands. Note dolichocephaly, an asymmetric face with slight hypertelorism, apparently low-set right ear, small mandible, and positional anomalies of the fingers.

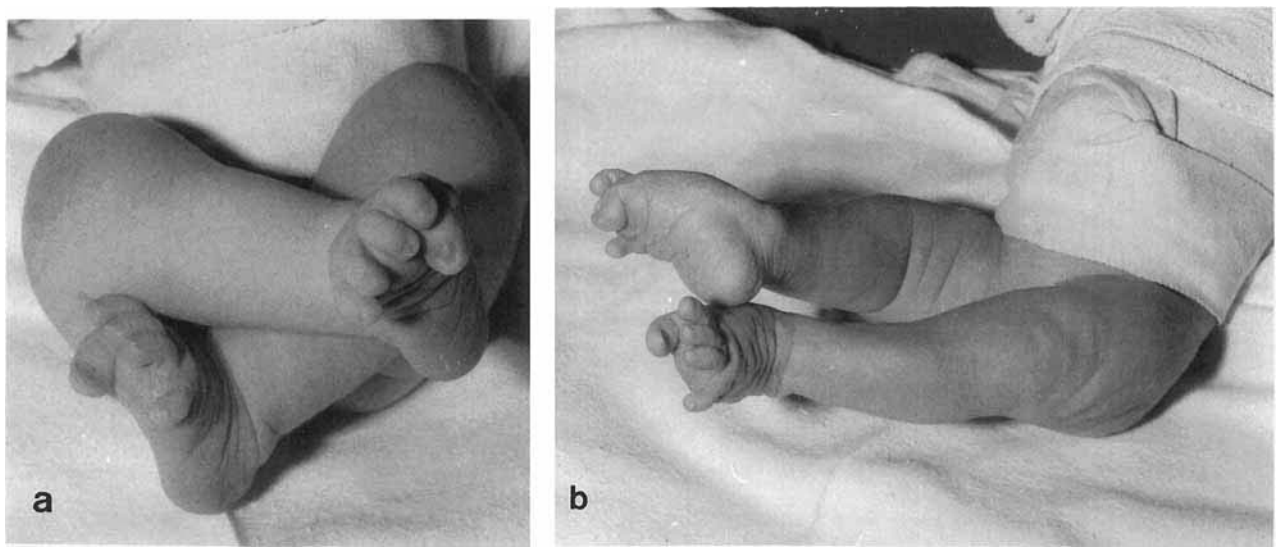

Fig. 3. **a,b:** Patient 2, lower limbs. Note bowing, and malposition of feet and toes. There are cutaneous dimples at the outer aspects of the ankles, on the right more so than on the left.

Fig. 4. **a:** Patient 1. Relatively broad femora and tibiae with different and somewhat asymmetrical degrees of bowing, or angulation, only slight bowing of fibulae, and malposition of the feet. Also present are cortical thickening of the medial aspects of the midshaft of femora and tibiae; vertical radiolucencies in the metaphyseal regions; and distal femoral and proximal tibial epiphyses. **b:** Patient 2. Comparable alterations as in patient 1.

Fig. 5. Right leg. **a:** Patient 1. Pronounced anterior bowing of the tibia. Minimal anterior curving of the fibula. **b:** Patient 2. Analogous but milder bowing.

recent reviews and classification of the distal arthrogryposes do not mention SWS [Bamshad et al., 1995].

Indeed, we are unaware of other publications since ours [Stüve and Wiedemann, 1971a, b] devoted specifically to a further delineation of SWS. Spranger and Maroteaux [1990b] state that they have observed 9 additional SWS cases, and Maroteaux [personal communication] and Meinecke (personal communication) mention further observations. It seems highly desirable that these and other unpublished cases be reported as soon as possible so as to speed syndrome delineation and identification. The entry in the third edition of Maroteaux [1995] is a most welcome start in that direction, as is the paper by Kozlowski [1996] in this Festschrift.

Thus, we characterize SWS as Multiple Congenital-anomalies (MCA) syndrome of shortness of stature, bowing of lower limbs, camptodactyly, respiratory distress/apneic spells, and hyperthermic episodes frequently associated with dysphagia/feeding/swallowing difficulties. Radiologically, the skeletal changes are quite different from those seen in campomelic syndrome in that the long bones are short and thick with large metaphyses. The angulation of the femora and tibiae is quite sharp and associated with internal thickening of the cortex in the concavity of the bend. This is a severe disorder, with most infants dying in the first few days of life of respiratory problems and/or hyperthermia. Maroteaux [personal communication] has personal experience with an affected infant who lived longer than 2 months. We are concerned that long-term survivors with SWS may manifest mental retardation and/or signs of neurologic damage; in the case of Kozlowski [1996], psychomotor development is slightly delayed. That boy is alive and well at age 3½ years, after surviving several episodes of pyrexia before age 2 years.

Involvement of double first cousins (see Fig. 1) is strong evidence for autosomal-recessive inheritance.

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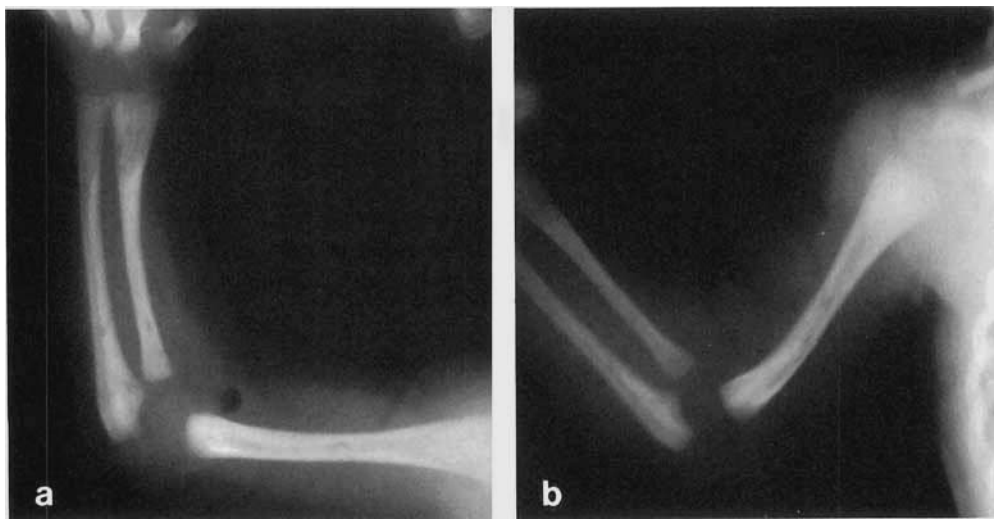

Fig. 6. **a,b:** Mild or minimal bowing of long bones of the arms; vertical radiolucencies in metaphyseal regions. Metacarpal 1 is short.

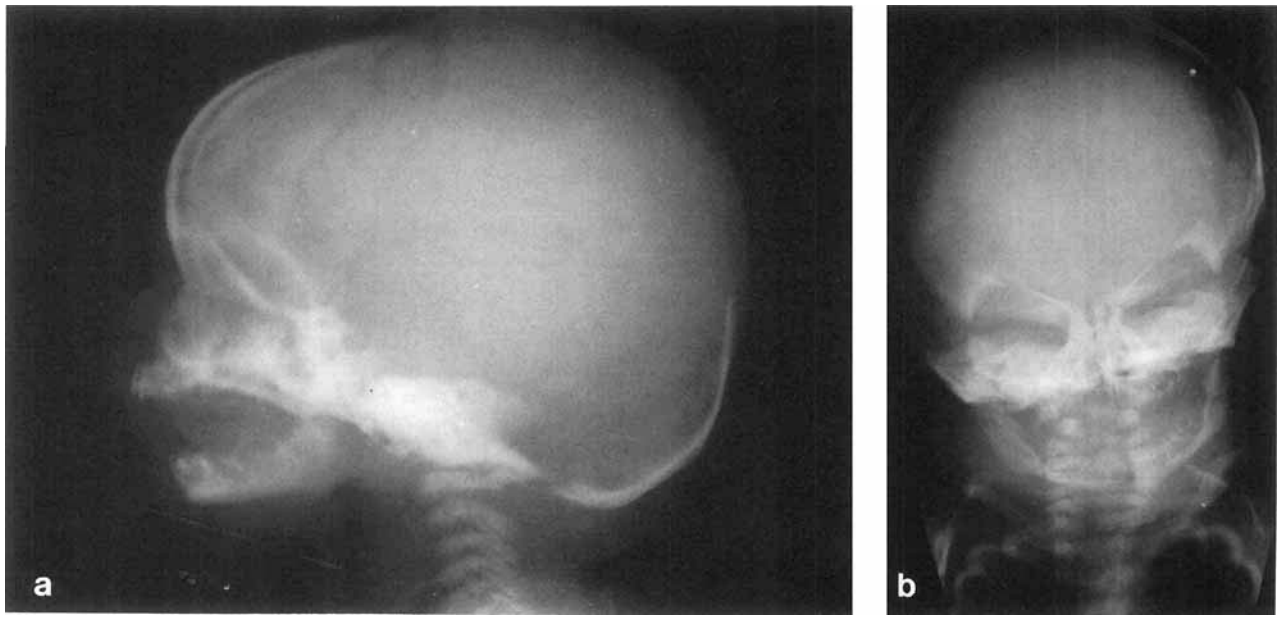

Fig. 7. **a:** Patient 1. Lateral skull radiograph. Dolichocephaly with frontal dysplasia, unossified parietal calvaria, and hypoplasia of mandible. **b:** Patient 2. Frontal skull radiograph. Plagiocephaly; mildly hypoplastic mandible.

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